TENT COOPERATION TRE Y

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 16 May 2000 (16.05.00)	
International application No. PCT/GB99/03172	**Applicant's or agent's file reference** MCG/P76519 WO
International filing date (day/month/year) 22 September 1999 (22.09.99)	**Priority date** (day/month/year) 23 September 1998 (23.09.98)
Applicant FLYNN, Richard, Anthony et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

18 April 2000 (18.04.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer S. Mafla
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

GB9903172

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

GREEN, Mark, Charles
Urquhart-Dykes & Lord
30 Welbeck Street
London W1M 7PG
ROYAUME-UNI

Date of mailing (day/month/year)
08 June 2000 (08.06.00)

Applicant's or agent's file reference
MCG/P76519 WO

IMPORTANT NOTIFICATION

International application No.
PCT/GB99/03172

International filing date (day/month/year)
22 September 1999 (22.09.99)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address
GREEN, Mark, Charles
Urquhart-Dykes & Lord
91 Wimpole Street
London W1M 8AH
United Kingdom

State of Nationality:
State of Residence:
Telephone No.: 020 7629 1771
Facsimile No.: 020 7491 1216
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
GREEN, Mark, Charles
Urquhart-Dykes & Lord
30 Welbeck Street
London W1M 7PG
United Kingdom

State of Nationality:
State of Residence:
Telephone No.: 020 7487 1550
Facsimile No.: 020 7487 1599
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office'
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
A. Karkachi

Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

003339689

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
MCG/P76519 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/03172	22/09/1999	23/09/1998
International Patent Classification (IPC) or national classification and IPC A61K9/12		
Applicant PHARMAX LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18/04/2000	19.09.2000
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Boulois, D Telephone No. +31 70 340 3878

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/03172

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-15	as originally filed			
4a	as received on	19/07/2000	with letter of	17/07/2000

Claims, No.:

1-28	as received on	19/07/2000	with letter of	17/07/2000

Drawings, sheets:

1/3-3/3	as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-28
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-28
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-28
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:
D1: WO-A-9820836
D2: J. of Clinical Pharmacology and the J. of new drugs, 1970(10),274-281
D3: Archives of Disease in Childhood, 68,1993, 788-792

2. The present application satisfies the criterion set forth in Articles 33(2) and 33(3) PCT because the subject-matter of Claims 1-28 is new and involves an inventive step in respect of the prior art.

2.1. The document D1 discloses aerosol compositions of colimycine M, which corresponds to colistine sulphomethate (see D1 page 6, line 36- page 7, 36; page 8, l. 3-13; page 11, l. 11-20; page 20, line 35 - page 22, line 34). This document refers to powder aerosol of colimycin (see D1, page 22, lines 19-20), but only discloses explicitly a liquid aerosol (see D1, pages 57,58,61, examples 11,12 and 17). This document teaches away from the use of a powder aerosol of colimycine (see D1, page 22, lines 19-34; page 24, lines 4-13). The example 17 of D1 discloses liquid aerosols which have the claimed size obtained after nebulization of the liquid.

The document D2 discloses lyophilized forms of colistimethate without thiomersol, dibucaine and citrate buffer (see D2, page 274). There is no size of the powder given in D2, and the size of 1-7 microns is obtained by the action of the "positive pressure breathing instruments" on the liquid compositions of colistimethate (see D2 page 276, right column).

The document D3 relates also to liquid aerosol compositions of colistin sulphomethate having a size of 0.5-5 microns obtained by nebulization of the liquid composition (see D3, page 790, left col.; page 791, left col.). No powder form of the claimed size is disclosed in D3.

2.2 Documents D1, D2 or D3, which can all be considered to represent the most relevant state of the art, disclose aerosol compositions of colistimethate in liquid form,

and not in powder form of micronized active.
The problem to be solved by the present invention may therefore be regarded as how to avoid the problem of coldness of the spray, the evaporation of water, and the increase of concentration of the active with time (see the present application, page 3).
The solution proposed in the present application is considered as involving an inventive step (Article 33(3) PCT), because the problem was not mentioned in the prior art, D1 even teaching away from using a powder aerosol (see D1, page 22, lines 19-34; page 24, lines 4-13), and because the prior art documents do neither disclose, nor suggest the use of colistimethate in powder form for an aerosol. Consequently, the subject-matter of claims 1-28 is inventive over D1, D2 and D3 (Article 33(3) PCT.

Re Item VIII
Certain observations on the international application

Claims 26-28 do not meet the requirements of Article 6 PCT, because their subject-matter is redundant with the subject-matter of claims 1-3.

WO-A-98/20836 is to be noted as the international publication which is equivalent to US-A-5,767,068.

J. of Clinical Pharmacology and the J. of New drugs, 1970(10),274-281, describes sodium colistimethate aerosols for use in the treatment of gram-negative infections of the respiratory tract. The aerosol is prepared by dissolving sodium colistimethate sterile powder in sterile water. When administered through a suitable nebuliser the aerosol has a particle size of 1-7 microns.

Archives of Diseases in Childhood, 68,1993, 788-792, describes the treatment of cystic fibrosis using aerosols. The paper refers to the delivery of micronised gentamicin powder using a Rotahaler (registered trade mark). It was found that the powder caused coughing. The paper concludes that aerosol forms of drugs delivered through a nebuliser are more suitable for treatment of cystic fibrosis.

Summary of Invention

It has now been discovered that micronised colistin sulphomethate sodium can be administered to the airways of a patient using a powder dose inhalation device. The micronised

CLAIMS

1. Micronised particles of colistin sulphomethate sodium wherein at least 90% by volume of the micronised particles have a diameter of less than 10 micrometers for use in the treatment of a pulmonary infection by powder inhalation, wherein the colistin sulphomethate sodium is not separated into component form.

2. Colistin sulphomethate sodium for the use as claimed in Claim 1 wherein the micronised powder is mixed with a carrier.

3. Colistin sulphomethate sodium for the use as claimed in Claim 2 wherein the carrier is lactose.

4. A composition comprising micronised colistin sulphomethate sodium as defined in Claim 1 and a carrier, in the absence of free liquid.

5. A composition as claimed in Claim 4 wherein the carrier is lactose.

6. A composition as claimed in Claim 4 or Claim 5 wherein the ratio of colistin sulphomethate sodium to carrier is from 5:1 to 1:2 by weight.

7. A composition as claimed in Claim 4 or Claim 5 wherein the ratio of colistin sulphomethate sodium to carrier is from 4:1 to 1:1 by weight.

8. The composition as claimed in any one of Claims 4 to 7 wherein at least 50% by volume of the carrier particles have an effective particle size in the range of 30-150 micrometers.

9. A composition as claimed in any one of Claims 4 to 8 wherein at least 50% by volume of the micronised colistin sulphomethate sodium has a particle diameter of less than 8 micrometers.

10. A composition as claimed in any one of Claims 4 to 9 wherein at least 25% of the particles of micronised colistin sulphomethate sodium have a diameter of less than 6 micrometers.

11. A composition as claimed in any one of Claims 4 to 10 wherein the micronised colistin sulphomethate sodium is prepared in the desired particle size range using a fluid energy mill.

12. A process for the preparation of a composition as claimed in any one of Claims 4 to 11 which comprises mixing micronised colistin sulphomethate sodium and a carrier.

13. A pharmaceutical dosage form suitable for use with a dry powder inhaler comprising micronised colistin sulphomethate sodium wherein at least 90% by volume of the particles have a diameter less than 10 micrometers or a composition according to any one of Claims 4 to 11 and a container, said dosage having a content of below 10 wt % water.

14. A pharmaceutical dosage form according to Claim 13 wherein the container is a hard gelatin capsule.

15. A capsule containing micronised colistin sulphomethate sodium wherein at least 90% by volume of the micronised particles have a diameter of less than 10 micrometers.

16. A capsule as claimed in Claim 15 containing from 10 to 200 micrograms of micronised colistin sulphomethate sodium.

17. A capsule as claimed in Claim 15 containing from 30 to 150 milligrams of micronised colistin sulphomethate sodium.

18. A capsule as claimed in any one of Claims 15 to 17 further comprising a carrier.

19. A capsule as claimed in Claim 18 when the carrier is lactose.

20. A capsule according to any one of Claims 15 to 19 which is opaque.

21. A capsule according to any one of Claims 15 to 19 or a composition according to any one of Claims 4 to 11 packed in an opaque container.

22. A capsule containing micronised colistin sulphomethate sodium when the micronised particles have a diameter of less than 10 micrometers, in unit dosage form.

23. A capsule according to any one of Claims 15 to 22 which additionally comprises a micronised bronchodilatory drug.

24. A capsule according to Claim 23 wherein the bronchodilatory drug is salbutamol.

25. A capsule according to Claim 23 or Claim 24 which comprises from 50 to 150 milligrams of colistin sulphomethate sodium and from 1 to 250 micrograms of bronchodilatory drug

26. Micronised particles of colistin sulphomethate sodium wherein at least 90% by volume of the micronised particles have a diameter of less than 10 micrometers for use in the treatment of a pulmonary infection by powder inhalation, wherein the colistin sulphomethate sodium is not separated into component form.

27. Colistin sulphomethate sodium for the use as claimed in Claim 26 wherein the micronised powder is mixed with a carrier.

28. Colistin sulphomethate sodium for the use as claimed in Claim 27 wherein the carrier is lactose.

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(71) Applicant *(for all designated States except US)*: **PHARMAX LIMITED** [GB/GB]; Bourne Road, Bexley, Kent DA5 1NX (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **FLYNN, Richard, Anthony** [GB/GB]; 69 Chestnut Grove, Wilmington, Kent DA2 7PQ (GB). **GOLDMAN, Martin, Harris** [GB/GB]; 19 Myddelton Park, London N20 0HT (GB). **LOVELY, James, Richard** [GB/GB]; 65 Longridge Road, London SW5 9SG (GB).

(74) Agents: **GREEN, Mark, Charles** et al.; Urquhart-Dykes & Lord, 30 Welbeck Street, London W1M 7PG (GB).

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WO 00/16745 A3

(54) Title: MICRONISED PHARMACEUTICAL COMPOSITIONS

(57) Abstract: Pharmaceutical compositions are described comprising micronised colistin sulphomethate sodium. The micronised pharmaceutical may be used together with a carrier such as lactose. The pharmaceutical compositions may be packed into containers such as gelatin capsules and administered by powder inhalation.

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(71) Applicant *(for all designated States except US)*: PHARMAX LIMITED [GB/GB]; Bourne Road, Bexley, Kent DA5 1NX (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: FLYNN, Richard, Anthony [GB/GB]; 69 Chestnut Grove, Wilmington, Kent DA2 7PQ (GB). GOLDMAN, Martin, Harris [GB/GB]; 19 Myddelton Park, London N20 0HT (GB). LOVELY, James, Richard [GB/GB]; 65 Longridge Road, London SW5 9SG (GB).

(74) Agents: GREEN, Mark, Charles et al.; Urquhart-Dykes & Lord, 91 Wimpole Street, London W1M 8AH (GB).

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Published
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(54) Title: MICRONISED PHARMACEUTICAL COMPOSITIONS

(57) Abstract

Pharmaceutical compositions are described comprising micronised colistin sulphomethate sodium, The micronised pharmaceutical may be used together with a carrier such as lactose. The pharmaceutical compositions may be packed into containers such as gelatin capsules and administered by powder inhalation.

Applicant

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MICRONISED PHARMACEUTICAL COMPOSITIONS

The present application relates to improvements in or relating to pharmaceutical compositions comprising micronised colistin sulphomethate sodium.

Background and Prior Art

Colistin is an anti-bacterial cationic cyclic polypeptide belonging to the polymixin group. It is produced as a secondary metabolite of *Bacillus polymyxa* var. *colistinus*. Treatment of colistin base with formaldehyde and sodium bisulphite results in the production of colistin sulphomethate sodium. This is described in Japanese patent 4898/1957. The product is a crystalline powder which is soluble in water.

Colistin sulphomethate sodium is a combination of the negatively charged molecular ion colistin sulphomethate with positive sodium ions. It should be carefully distinguished from colistin sulphate. Both are described in the European Pharmacopoeia.

Colistin is of particular benefit in the treatment of serious infections caused by bacterial pathogens such as *Pseudomonas aeruginosa*, *Escherichia coli* and *Klebsiella sp.* An important property of colistin is that bacteria which are sensitive to the drug do not readily acquire resistance. Colistin as a pharmaceutical may be prepared into numerous different preparations, e.g. topical, bladder irrigation, oral such as tablets, or as intravenous or intra-muscular injections.

Colistin sulphate can be prepared from colistin. It is currently used to treat gram negative infections of the body such as intestinal infections due to various micro-organisms and, usually in association with other antibiotics, for the suppression of bowel flora. As noted above, colistin sulphate should be distinguished from colistin sulphomethate sodium.

Colistin sulphomethate sodium can also be prepared. It exists as a white to slightly yellow hygroscopic powder. It is commercially supplied at a particle size of 100-200 μm mass median diameter. The powder is highly soluble in water and as such is used for parenteral administration. As a powder, colistin sulphomethate sodium must be stored in air-tight containers, preferably protected from the light. Colistin sulphomethate sodium is used in the treatment of infections in patients suffering from cystic fibrosis, a genetic disease which affects many body systems, and which develops at a young age. Various glands of the body do not function properly. The disease is marked by a malfunction of the glands in the lining of the bronchial tubes. Instead of producing their normal thin mucus, the bronchial glands produce a thick, sticky mucus that stagnates in the tubes. Microbes are able to multiply readily, causing serious respiratory infections ultimately leading to respiratory failure. It is known that colistin sulphomethate sodium is effective in treatment of infections caused by these microbes e.g. *Pseudomonas aeruginosa*. The usual form of administration is as a solution for inhalation after nebulisation. The nebulised solution is prepared by taking a vial in which there is a known dosage of colistin sulphomethate sodium powder, injecting water into the vial and then inhaling the solution into the lungs through a nebuliser. Colistin

sulphomethate sodium is poorly absorbed into the bloodstream. This is preferred as the bacteria can be attacked in the mucus which lines the lungs during illness.

Whilst jet nebulisation therapy has been shown to be successful, the nebulisation technique has several drawbacks. Jet nebulisers utilise compressed gases (usually air) to convert a drug solution into a spray. The compressed air passes through a narrow venturi orifice and negative pressure is created. Liquid is drawn from a fluid reservoir through a feed tube, fragments into droplets, and is accelerated to a velocity sufficient for more than 99% of the droplet mass to impact on baffles or on the nebuliser where droplets coalesce and drain back into the fluid reservoir. Only 1% of the aerosol mass leaves the nebuliser directly. The outgoing air becomes saturated with water derived from liquid retained in the nebuliser, and this has two important consequences: Firstly, the nebuliser is cooled and reaches an equilibrium temperature approximately 10°C below ambient, so that the patient inhales a relatively cold spray. Secondly, the evaporation of water causes the concentration of solutes to increase with time.

There are many different designs of nebuliser available which use different flow rates of compressed gas. The output from these nebulisers will all be different and accordingly it is difficult for a patient to ensure that a constant dose is administered. The nebulisers themselves are bulky due to the compressors which are required. Although described as being transportable, the nebuliser/compressor system is not truly portable. When they are undergoing treatment, patients need to

remain connected to the mouthpiece of the nebuliser for approximately 20 minutes in order to complete the therapy and in order to ensure that the correct dose is administered. An electrical supply is needed to run the nebuliser.

It will be seen from the above that, although colistin sulphomethate sodium is a valuable pharmaceutical in the treatment of infections occurring during cystic fibrosis and other bacterial infections, there are a number of disadvantages which mean that it is not widely accepted as a treatment regime, particularly for infants. It has been determined that many of the problems arise from the preferred delivery method described above, i.e. as a nebulised liquid.

WO 95/00128 (Astra) describes the delivery to the lungs of dry powder polypeptides. An enhancer compound is used to promote absorption into the systemic circulation. In contrast, colistin sulphomethate sodium is used very locally in the lungs - absorption into the bloodstream is not an objective.

US-A-5,767,068 (Pathogenesis) describes the separation and use of individual components of colistin sulphate. Colistin sulphate is separated into individual components in free base form. Such components are described by Ebverdam, Larsen and Lund *(Journal of Chromatography, 218 (1981) 653-661)*.

Summary of Invention

It has now been discovered that micronised colistin sulphomethate sodium can be administered to the airways of a patient using a powder dose inhalation device. The micronised

colistin may be used alone or with a carrier, such as lactose.

According to the present invention, there is firstly provided the use of micronised colistin sulphomethate sodium in a method of treatment of the human body, particularly in the treatment of bacterial infections of the pulmonary system, most particularly in the treatment of secondary infections in patients suffering from cystic fibrosis, by powder inhalation.

According to a further aspect of the present application, there is provided a pharmaceutical composition comprising micronised colistin sulphomethate sodium and a carrier, in the absence of free liquid.

According to a yet further aspect of the present invention, there is provided a pharmaceutical dosage form suitable for use with a dry powder inhaler comprising micronised colistin sulphomethate sodium, optionally together with a carrier, and a container. The container is preferably a capsule.

Detailed Description

Micronised colistin sulphomethate sodium may be defined as being a powder wherein at least 90% by volume of the powder comprises particles have a diameter of less than 10 micrometers. Most preferably, at least 50% of the particles have a diameter of less than 8 micrometers. More preferably, at least 25% of the particles have a diameters of less than 6 micrometers.

Figure 1 shows a particle size analysis of micronised colistin sulphomethate sodium.

Medicaments for administration by inhalation should be of a controlled particle size in order to achieve maximum penetration into the lungs, a suitable particle size range being 0.01-10, usually 1-8 micrometers. Particle sizes may be measured by a number of methods, e.g. by laser diffraction or microscope analysis.

Micronised colistin sulphomethate sodium may be prepared by fluid energy milling, ball milling, spray drying or precipitation. The colistin sulphomethate sodium may be administered in conjunction with a carrier. The carrier may be any non-toxic material which is chemically inert to the colistin sulphomethate sodium and will be acceptable for inhalation or for administration. Examples of carriers which may be used include inorganic salts, e.g. sodium chloride or calcium carbonate; organic salts, e.g. sodium tartrate or calcium lactate; organic compounds, e.g. urea; monosaccharides, e.g. lactose, arabinose or dextrose; disaccharides, e.g. maltose or sucrose; polysaccharides, e.g. starches and dextrans. A particularly preferred carrier is a lactose, e.g. crystalline lactose.

The present invention also provides a method for preparing a composition of the invention which comprises mixing together micronised colistin sulphomethate sodium and a carrier. The colistin sulphomethate sodium and the carrier may be blended in a drum, hoop or Y-cone blender as known in the art.

The carrier does not have to have the same particle size specification as the colistin sulphomethate sodium. The carrier may in fact generally be of a larger particle size than

that of the colistin sulphomethate sodium in order to facilitate delivery from the inhalation device and yet not be deposited in the finer airways of the lungs. The inclusion of a carrier may ease dosage of pharmaceutical and carrier into capsules. Preferably at least 50%, and more desirably at least 70% by volume of the carrier particles have an effective particle size in the range of 30 to 150, especially 30 to 80, micrometers. The admixture of pharmaceutical and carrier may contain up to 75% by weight, more preferably up to 50% by weight of carrier. Generally the ratio of colistin sulphomethate sodium will be in the range of 5:1 to 1:2 preferably 4:1 to 1:1 by weight.

Colistin sulphomethate sodium is a negatively charged molecular ion with positively charged sodium counter ions. Figure 2 shows the structure. There are five sulphomethate groups (CH_2-OSO_2^-). In contrast, Pathogenesis are producing a neutral base shown in Figure 3. US-A-5,767,068 refers to variable groups R_1 and R_2; R_1 is identified as 6-methyloctanoyl or 6-methylheptanoyl, and R_2 as sec-butyl, isobutyl or isopropyl.

It has now been surprisingly found that the negatively charged colistin sulphomethate ion (preferably in its sodium form) can be delivered to the lungs. As absorption into the blood stream is not wanted, the negatively charged ion is preferred to the base colistin.

It has been found that colistin sulphomethate sodium is a mixture of at least ten components. Tests carried out on mixtures of antibacterial preservatives show that the mixture

of components found in colistin sulphomethate sodium show synergy of activity against gram negative microbial organisms.

It has been surprisingly found that water absorption of a micronised powder is comparatively low, e.g. approximately 5-7% by weight under normal atmospheric conditions. It has also been found that the micronised powder does not stick together. In powders having a larger particle size, the particles can stick together because of static forces. This sticking occurs will colistin and colistin sulphate. However, this is not found in the colistin sulphomethate sodium of the present invention. This is a further surprising advantage of the present application.

In addition to the micronised colistin sulphomethate sodium and, optionally, the carrier, the composition may contain other ingredients, such as colouring matter or flavouring agents such as saccharine, which may be present in inhalant compositions. Antistatic agents may also be added, e.g. as described in GB-A-2269992 (Rhone-Poulenc Rorer Ltd). It is preferred to use the minimum of such other ingredients.

The powder formulation may contain other pharmaceutical ingredients such as bronchodilators e.g. salbutamol Such other pharmaceutical ingredients preferably have an effective particle size similar to that of the colistin. The bronchodilatory drug will be delivered in very small (microgram) quantities. For example a capsule may contain from 50 to 150, e.g. 125, milligrams of colistin sulphomethate sodium and from 1 to 250, e.g. 200, micrograms of salbutamol.

The micronised powder may be delivered to the lungs through a specialised powder inhalation device. Most preferred is location of the powdered pharmaceutical within a hard capsule or a blister package. The capsule or blister is ruptured or broached within the inhaler device, thereby enabling the powder to be inhaled through the mouthpiece as air is sucked in.

There is also provided, therefore, as a further feature of the invention, a dosage unit comprising a capsule containing colistin sulphomethate sodium, preferably in the form of a pharmaceutical composition of the present invention. The capsule may be formed of gelatin or a plastics material.

By carefully controlling the conditions under which capsules and blisters and filled, the final moisture level in the product can be kept to below 15 wt %, preferably below 5 wt %. The humidity level is preferably below 25% RH, most preferably below 15% RH. The low moisture level is important for product stability, and enables the product to be filled with minimal static effects. Flow out of the capsule or blister is also improved.

By careful selection of capsule and packaging components, stability and dosing can be controlled. The level of lubricant is kept low (preferably below 0.2% wt %). Capsules for oral use usually contain 2-3 wt % lubricant. Mould lubricant could interact with the dry powder. Capsule integrity is important, and accordingly a peelable lid to the blister package is preferred to a conventional "push out" seal. The blister may be, e.g. aluminium (40-50 μm thick) laminated with PVC (50-70 μm thick) and PA (20-30 μm thick). The peelable seal may be

formed of soft aluminium (18-22 μm thick) laminated with PE7 (20-25 μm thick).

The amount of composition contained in the capsule will, of course, depend upon the desired dosage. However, the capsule suitably contains from 10 to 200 milligrams, most preferably 30 to 150 milligrams of the colistin sulphomethate sodium.. The colistin sulphomethate sodium may be delivered with or without a carrier. If a carrier is used then clearly a larger amount of the mix of carrier and pharmaceutical is required. It has been found that the capsule should contain a larger dose of drug than the amount which will actually be delivered to the lungs. Dosages are usually expressed in "units". 80 mg of colistin sulphomethate is equivalent to approximately 1 million units of colistin sulphomethate. One unit of colistin sulphomethate is contained in 0.00007874 mg of the first International Reference Preparation (1966) of colistin sulphomethate. Children with cystic fibrosis may be treated with nebulised colistin sulphomethate sodium at a level of 500,000 units, twice daily. The respirable fraction from a conventional nebuliser (CR 50 System 22) is approximately 9 mg of colistin sulphomethate sodium from a 500,000 unit dose. This can be tested using a multistage impinger and measuring mass collected at stages 3 and 4.

A preferred device for delivering the pharmaceutical composition according to the present invention is the Turbospin (Registered Trade Mark) originating from PH & T. This device uses a gelatin capsule which is pierced in the bottom by a single metal needle. When the patient inhales through the mouthpiece, air is drawn in through the tangentially ranged

Preferred devices

slits around the chamber. This spins the capsule and throws out the contents into the airstream. A flip top on the device allows up to three spare capsules to be stored. Another preferred device for delivering the pharmaceutical composition is the Aerohaler (Registered Trade Mark) from Boehringer Ingelheim. This device uses a hard gelatin capsule which is pierced by two metal needles in the side of a capsule. When the patient inhales through the mouthpiece, air enters the bottom of the chamber causing the capsule to spin and throw out its contents into the airstream. The unit holds six capsules in a carousel cartridge. When all six capsules have been used, the unit locks and it must be re-loaded. Other devices known in the art for delivery of encapsulated powders by inhalation can be used.

The capsule keeps the powder dry and thus in flowable form. The capsules should preferably be designed to protect their contents from light, e.g. they should be opaque or the capsules may be packed and/or stored in opaque containers, e.g. coloured or covered containers, or metal foil.

The invention is further described by reference to the following Examples, illustrated by the following figures.

Figure 1 shows a particle size analysis of micronised colistin sulphomethate sodium.

Figure 2 shows the structure of colistin sulphomethate with accompanying sodium ions.

Figure 3 shows a neutralised colistin base, as described in US-A-5,767,068.

Examples

Example 1

Micronised colistin sulphomethate sodium was produced by fluidised energy milling using a Hosokawa Alpine mill of powdered colistin sulphomethate sodium having an average particle size of approximately 100 μm supplied by Dumex Pharmaceuticals. A sample of the micronised colistin sulphomethate sodium was suspended in chloroform and the particle size analysed by a laser counter. Figure 1 shows the range of particle sizes of the micronised colistin.

Example 2

Gelatin pharmaceutical capsules (standard size 2) were obtained from Shionogi Qualicaps. The capsules were filled using a standard dosator (Zanassi LZ64) under controlled temperature and humidity conditions (17°C/10%-15% RH). Colistin sulphomethate sodium was filled into the capsules either as pure micronised powder or together with a lactose carrier (lactose monohydrate lactochem pharmaceutical grade from Borculo Whey Products). The fills are as shown on Table 1.

TABLE 1

Run Number	Mix Used	Total Fill
1	Colistin	125 mg
2	Colistin/Lactose (1:1)	165 mg
3	Colistin/Lactose (2:1)	140 mg
4	Colistin/Lactose (4:1)	130 mg
5	Colistin	125 mg

When colistin sulphomethate sodium is used alone, it flows well. Filling weights are standard. If a mixture of colistin to lactose as in Run 2 is used then the mixed powder flows well through the machine but there is sticking of the components of the dosator. Sticking reduces in Runs 3 and 4. Tests found respirable fractions in the region of 16 to 20 mg. This is the mass of colistin sulphomethate sodium collected on stages 3 and 4 of the multistage liquid impinger and equates to particles having a size less than about 3 to 4 micrometers.

Example 3

Filled capsules produced from Runs 1 to 4 above were stored for nine months under various humidity conditions. There was no degradation or clumping of the colistin sulphomethate sodium. There was no noticeable clumping of colistin sulphomethate sodium on the capsule walls.

Tests

Clinical trials were carried out. In one trial, the absorption of the powdered colistin sulphomethate sodium into the airways of the lungs was measured (specific airway conductance). It was found that 80% of patients, inhaling the micronised dry powder colistin sulphomethate sodium, were able to mobilise 80 mg of the drug, i.e. 1 mega unit. This is a very high uptake, and more than would be expected from a powdered drug. The powder does not cause irritation, and thus construction, of the lungs.

In a second trial, patients were given a premedication dose of 200 micrograms of salbutamol. This appeared to improve airway conductance.

In an alternative medication regime, the salbutamol can be mixed into the same capsule as the colistin sulphomethate sodium.

A further trial compared specific airway conductance, as measured by whole body plethysmography, of traditional nebulised colistin sulphomethate sodium and dry powder. There did not seem to be any noticeable difference.

CLAIMS

1. The use of micronised particles of colistin sulphomethate sodium wherein at least 90% by volume of the micronised particles have a diameter of less than 10 micrometers in the treatment of a pulmonary infections by powder inhalation, wherein the colistin sulphomethate sodium is not separated into component form.

2. The use of colistin sulphomethate sodium as claimed in Claim 1 wherein the micronised powder is mixed with a carrier.

3. The use of colistin sulphomethate sodium as claimed in Claim 2 wherein the carrier is lactose.

4. A composition comprising micronised colistin sulphomethate sodium as defined in Claim 1 and a carrier, in the absence of free liquid.

5. A composition as claimed in Claim 4 wherein the carrier is lactose.

6. A composition as claimed in Claim 4 or Claim 5 wherein the ratio of colistin sulphomethate sodium to carrier is from 5:1 to 1:2 by weight.

7. A composition as claimed in Claim 4 or Claim 5 wherein the ratio of colistin sulphomethate sodium to carrier is from 4:1 to 1:1 by weight.

8. The composition as claimed in any one of Claims 4 to 7 wherein at least 50% by volume of the carrier particles have an effective particle size in the range of 30-150 micrometers.

9. A composition as claimed in any one of Claims 4 to 8 wherein at least 50% by volume of the micronised colistin sulphomethate sodium has a particle diameter of less than 8 micrometers.

10. A composition as claimed in any one of Claims 4 to 9 wherein at least 25% of the particles of micronised colistin sulphomethate sodium have a diameter of less than 6 micrometers.

11. A composition as claimed in any one of Claims 4 to 10 wherein the micronised colistin sulphomethate sodium is prepared in the desired particle size range using a fluid energy mill.

12. A process for the preparation of a composition as claimed in any one of Claims 4 to 11 which comprises mixing micronised colistin sulphomethate sodium and a carrier.

13. A pharmaceutical dosage form suitable for use with a dry powder inhaler comprising micronised colistin sulphomethate sodium wherein at least 90% by volume of the particles have a diameter less than 10 micrometers or a composition according to any one of Claims 4 to 11 and a container, said dosage having a content of below 10 wt % water.

14. A pharmaceutical dosage form according to Claim 13 wherein the container is a hard gelatin capsule.

15. A capsule containing micronised colistin sulphomethate sodium wherein at least 90% by volume of the micronised particles have a diameter of less than 10 micrometers.

16. A capsule as claimed in Claim 15 containing from 10 to 200 micrograms of micronised colistin sulphomethate sodium.

17. A capsule as claimed in Claim 15 containing from 30 to 150 milligrams of micronised colistin sulphomethate sodium.

18. A capsule as claimed in any one of Claims 15 to 17 further comprising a carrier.

19. A capsule as claimed in Claim 18 when the carrier is lactose.

20. A capsule according to any one of Claims 15 to 19 which is opaque.

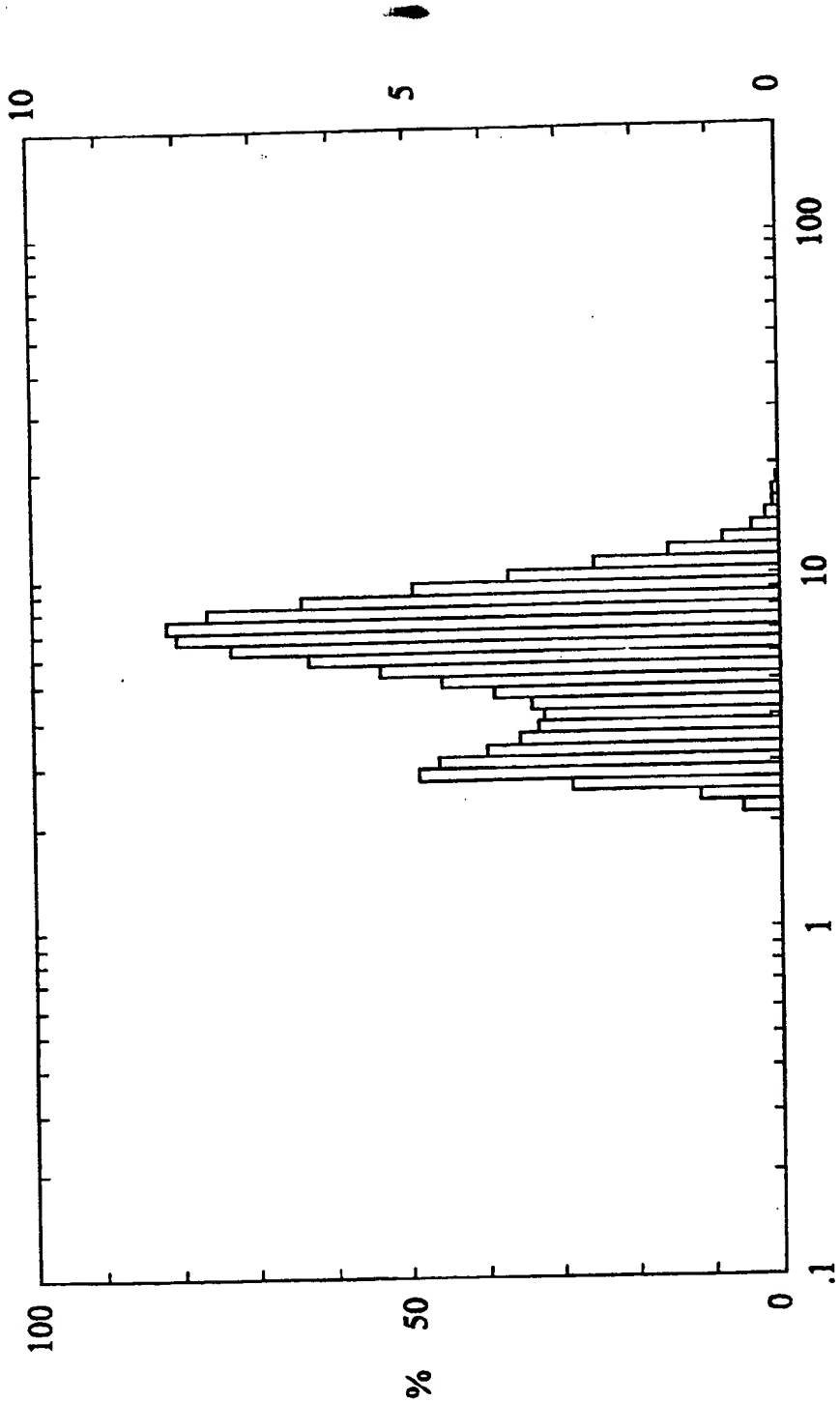
21. A capsule according to any one of Claims 15 to 19 or a composition according to any one of Claims 4 to 11 packed in an opaque container.

22. A capsule containing micronised colistin sulphomethate sodium when the micronised particles have a diameter of less than 10 micrometers, in unit dosage form.

23. A capsule according to any one of Claims 15 to 22 which additionally comprises a micronised bronchodilatory drug.

24. A capsule according to Claim 23 wherein the bronchodilatory drug is salbutamol.

25. A capsule according to Claim 23 or Claim 24 which comprises from 50 to 150 milligrams of colistin sulphomethate sodium and from 1 to 250 micrograms of bronchodilatory drug.



Particle sizing of micronised colistin sulphomethate sodium

FIG. 1

FIG. 2

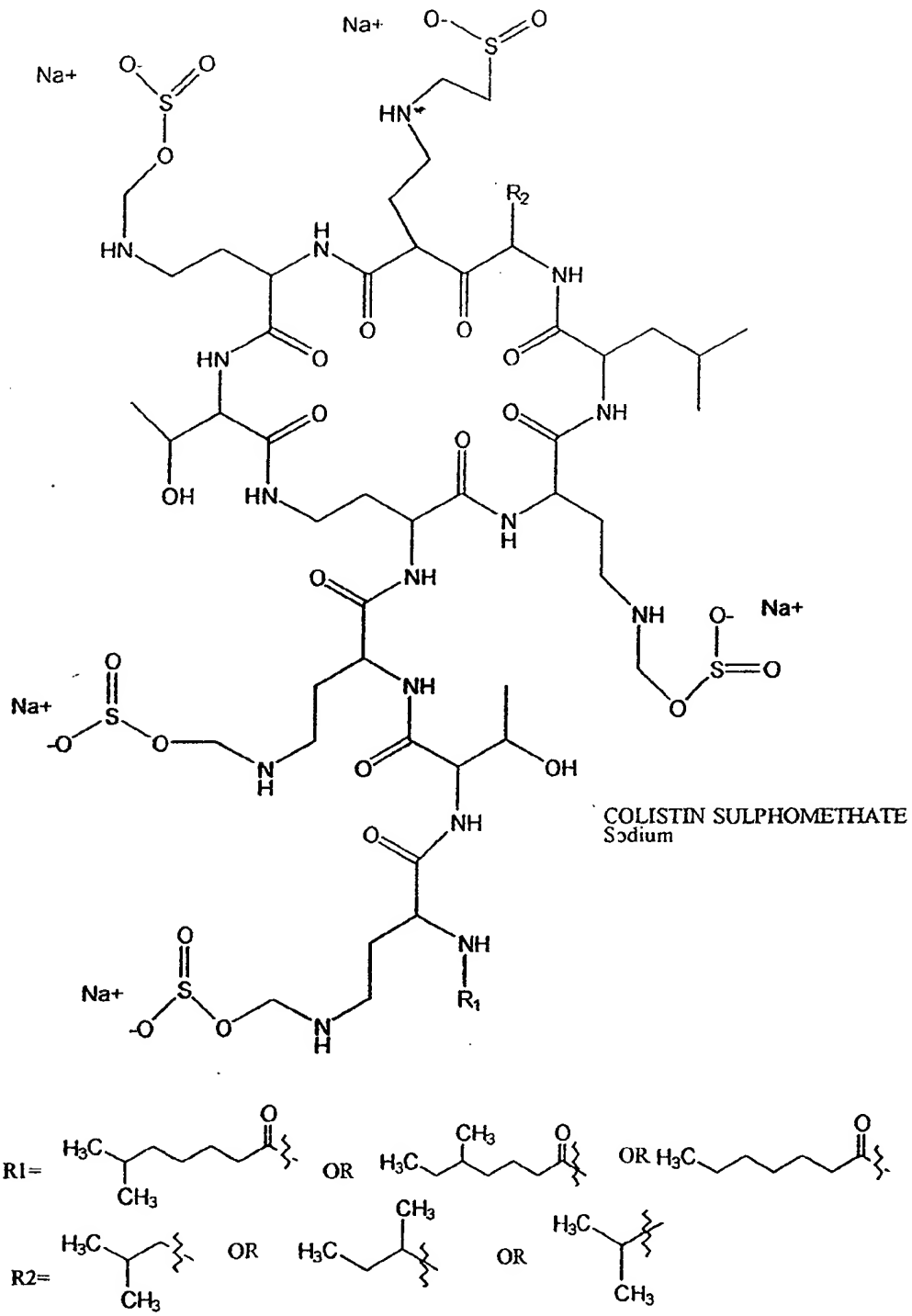
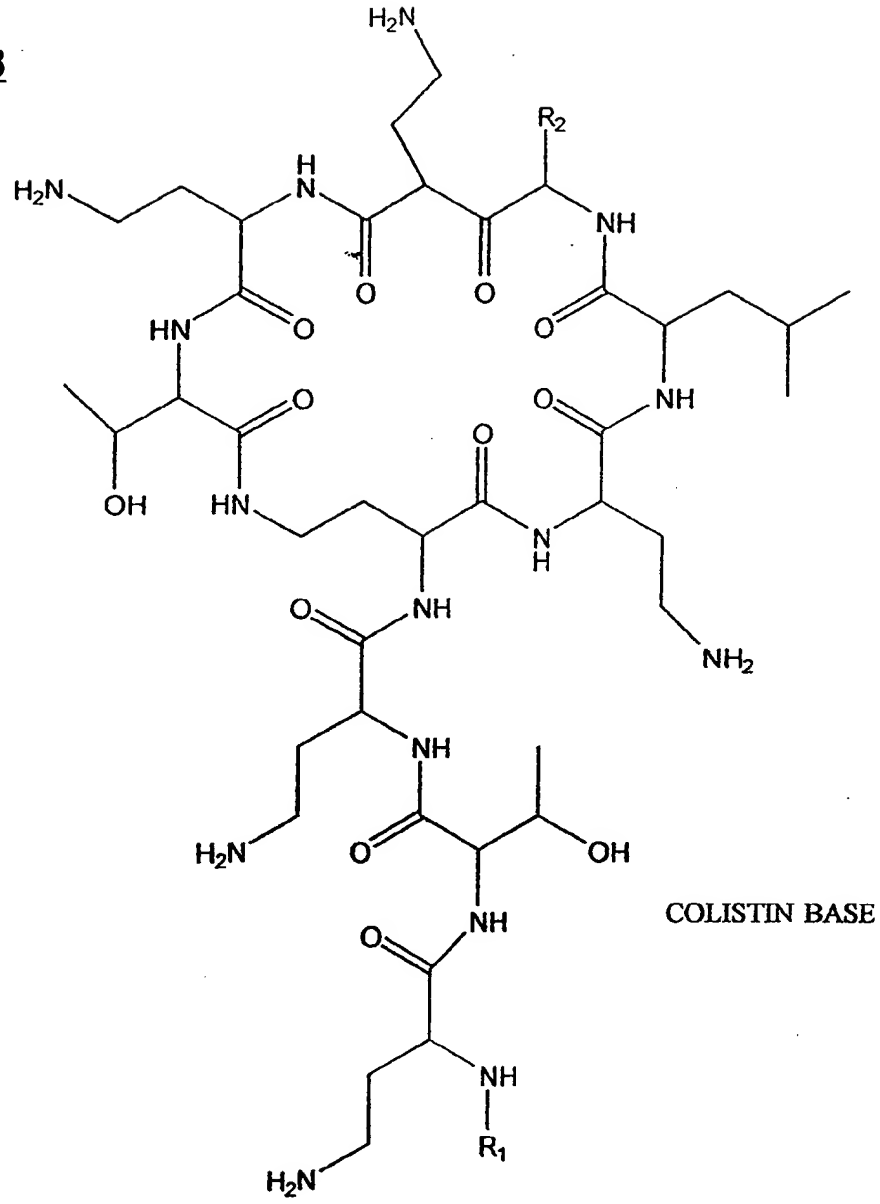
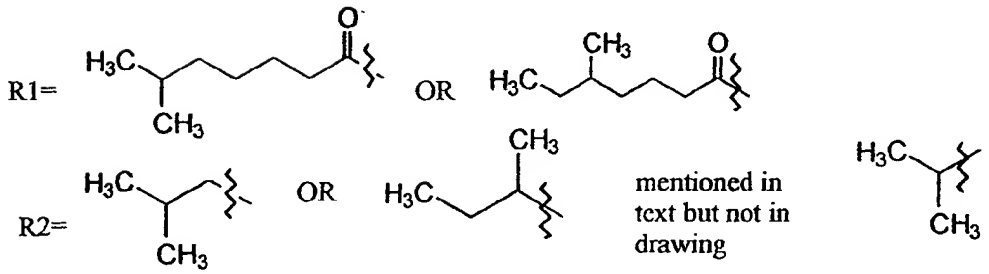


FIG. 3



COLISTIN BASE



INTERNATIONAL SEARCH REPORT

Inter 'onal Application No
PCT/GB 99/03172

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/12 A61K9/14 A61K31/7036 A61K38/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 20836 A (PATHOGENESIS CORP) 22 May 1998 (1998-05-22) page 6, line 36 -page 7, line 36 page 8, line 3 - line 13 page 11, line 12 - line 20 page 20, line 35 -page 22, line 34	1-25
A	ROSE H. D. ET AL: "Evaluation of Sodium Colistimethate aerosol in gram negative Infections of the respiratory Tract" J. OF CLINICAL PHARMACOLOGY AND THE J. OF NEW DRUGS, vol. 10, no. 4, 1970, pages 274-281, XP000901745 the whole document	1-25

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 April 2000	19/04/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Boulois, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter 'onal Application No
PCT/GB 99/03172

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	LITTLEWOOD J.M. ET AL: "Aerosol antibiotic treatment in cystic fibrosis" ARCHIVES OF DISEASE IN CHILDHOOD, vol. 68, 1993, pages 788-792, XP000901743 the whole document	1-25

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

national application No.
PCT/GB 99/03172

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-3 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

formation on patent family members

Inter ional Application No
PCT/GB 99/03172

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9820836 A	22-05-1998	US 5821623 A	13-10-1998
		AU 5790998 A	03-06-1998
		CA 2242335 A	22-05-1998
		EP 0920324 A	09-06-1999